Best Practice

TOPICS IN REVIEW

Vaccines in the 21st century

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Vaccination against infectious diseases has literally transformed the planet. It has succeeded in the elimination of smallpox and the near elimination of polio as scourges of humankind. This kind of success, as well as the great increase in understanding of immunology and the development of new technologies, has increased the hope that new vaccines will target other diseases. Indeed, expectations have been raised so much that vaccines are now being developed not just to prevent infectious diseases but to cure them. In addition, some conditions have now been shown to be related to infectious diseases—for example, human papillomavirus infection has been implicated in cervical cancer and Helicobacter pylori in gastritis, peptic ulcer disease, and stomach cancer—and vaccines should help to prevent or treat these diseases. Other clinical diseases or conditions are also now considered within the purview of vaccines. These include cancers (even those without a known infectious etiologic component), allergies, autoimmune diseases such as diabetes, metabolic diseases such as hyperlipidemias that lead to atherosclerosis and coronary artery disease, and even addictions such as cocaine and nicotine dependencies.

An examination of the recent advances in immunology and vaccinology provides insights into future vaccine developments. Great strides have been made in understanding how the body distinguishes self from non-self—that is, how the immune system recognizes a pathogen as being foreign and hence a target for killing. This is likewise important for understanding why the immune response sometimes becomes too active, resulting in allergies or autoimmune disease. By understanding which cells become activated and knowing what the triggers are, we can try intentionally to stimulate, alter, or suppress the responses.

Summary points

- New vaccines are being developed for treatment as well as prophylaxis
- Elucidation of how immune system cells process and then recognize and respond to antigens has prompted the development of new technologies to try to mimic or even improve on these responses
- New approaches try to induce specific types of immunity against selected structures rather than the whole virus
- Researchers are also trying to find ways of delivering antigen specifically to activate the body's T cell response
- Efforts to harness the immune response and turn it in another direction are also being used to make vaccines for allergies, autoimmune diseases, metabolic diseases, and addictions

The elucidation of how immune system cells process and then recognize and respond to antigens derived from pathogens has prompted the development of new technologies to try to mimic or even improve on these responses. Thus, whereas most existing vaccines were made simply and successfully by administering the pathogen in a weakened, killed, or dissected form, new approaches are much more "surgical." That is, they attempt to induce specific types of immunity (particularly cellular responses or particular classes of antibody) and against selected structures, rather than against the whole virus or bacterium or those parts that could easily be purified. In addition, the ability to sequence the genome of whole organisms has provided a new tool for identifying which proteins from a pathogen to include in a vaccine. Additionally, more effort is being applied to generating specific regional immunity at the site most relevant to prevent either infection (for example, mucosal surfaces) or disease.

Possibly the most intriguing revelations have been in the field of cellular immune responses—specifically, insights into how T cells recognize their targets and what occurs to the antigen in the target cells to make it into a form that can activate T cells. It has been recognized that a number of pathogens, for which we do not have vaccines, as well as immunotherapies for cancer, would require the generation of these T cells to prevent, limit, or treat disease. Earlier vaccine technologies may not be effective for generating these responses or may be considered problematic from a safety perspective for a given disease. For example, although live attenuated virus vaccines are quite effective for a number of diseases, they may in some instances revert to wild type virulence (for example, polio). Thus, using an attenuated HIV strain as a vaccine for HIV is considered by many to be too risky. Armed with an increased understanding of what is required to generate T cell response, "vaccinologists" have focused on finding ways to deliver antigen specifically to activate these T cells.

TECHNOLOGIES

Thus, insights into disease etiology and pathogenesis and the development of new technologies that enable vaccinologists to capitalize on new immunologic insights have been critical for this effort in new vaccines. Specific examples of new vaccine developments are given below as illustrations of various issues.

Recombinant DNA technology

The first example of a technology that has had an impact on vaccine development is recombinant DNA technology. Cloning has enabled the production of an effective hepatitis B vaccine that does not require the manufacture or purification of the intact or infectious virus. Other molecular biology tools have made it possible to identify which proteins are conserved among different strains of a virus or bacteria, or which are responsible for virulence of pathogens or oncogenesis in tumors. These proteins may be good candidates for vaccines.

Molecular attenuation of pathogens

Recombinant DNA technology has further resulted in the ability to manipulate genes so that, rather than relying on blind serial growth of viruses or bacteria in an effort to weaken them for use as live vaccines, pathogens can be attenuated or altered molecularly so that they are unable to effectively replicate or cause disease. For example, BCG is a live mycobacterium used in many countries as a vaccine against primary tuberculosis, but its effectiveness varies widely. This is partly because of the different derivations of different vaccine strains. Certain mutants, such as auxotrophic mutants, have been made through manipulation of the Mycobacterium tuberculosis genome, which results in the production of strains that cannot replicate unless they are provided with particular nutrients that would not be present in a human.[1] Likewise, salmonella and shigella strains are being attenuated molecularly so that they will still infect via the mucosal route, but will not be able to replicate.[2] Thus, by eliminating precisely and molecularly the pathogenicity from the pathogen, new vaccines may be made safer and more effective.

Vectors

Furthermore, a gene from a pathogen can be inserted into an innocuous agent so that the antigen can now be delivered in the form of a gene via an unrelated and nonpathogenic virus or bacteria. This technology is being used for attenuated versions of BCG, Salmonella, and Shigella. Vaccinia and a bird version of pox virus are also being evaluated as vectors for delivering the gene of a heterologous virus (notably HIV) in continuing clinical trials.[3]

A new type of vector that should enter clinical trials in the next few years for HIV and hepatitis C virus is based on the class of positive stranded RNA viruses known as alphaviruses.[4] These vectors provide several attractive features. They replicate by making multiple copies of mRNA encoding the structural proteins. Thus, when used as a heterologous expression vector, they cause the cell to make large quantities of the protein antigen quite rapidly. The replicon particle seems to be a normal viral particle on the outside, and hence can use some of the strategies that the wild-type virus uses for infecting cells efficiently. However, its genome has been altered so that the cell can produce the antigen for the vaccine but not the replicon structural proteins, and thus the cell cannot make any progeny virus. These particles, when made from certain strains of alphavirus, have the capability of targeting specialized immune cells called dendritic cells, which function to present antigen to stimulate cytotoxic T lymphocytes.

DNA vaccines

DNA vaccines, which are simply a bacterial plasmid encoding an antigen, are an even simpler form of gene vaccine that has been developed recently. These DNA vaccines have entered into clinical trials for a number of diseases such as HIV, malaria, and cancer.[5] DNA vaccines have generated considerable interest because they are simple and there is no need to make an intact virus or bacterium. Efforts to increase their potency are ongoing.

METHODS OF DELIVERY

Live poliovirus vaccines administered orally are the greatest current example of a practitioner- and user-friendly, economically feasible, and clinically effective vaccine. Given all of these attributes and the fact that most pathogens enter the host via a mucosal surface, vaccine development efforts have focused heavily on finding ways of delivering many types of antigens to the mucosa with and without the use of a live organism.

A new vaccine for influenza is based on the development of influenza strains that grow well only in the cooler temperatures of the nasal passages, but do not replicate in the warmer lower respiratory tract. This vaccine has been shown to be effective in children and adults after intranasal administration.[6,7] Non-living systems utilizing adjuvants (such as molecularly attenuated toxins from bacteria) are also being developed. An example of this is LTK63, a heat labile toxin of Escherichia coli, which has been made recombinantly with specific mutations to eliminate its toxic ability.[8,9] It has none of the toxic activity of the native protein, yet is a powerful adjuvant when coadministered with antigens in preclinical studies.

Oral delivery is an even more attractive route of administration from the patient's perspective, and several approaches are being developed. One approach has been to encapsulate the vaccine in such a way that it survives the gastric passage and reaches the intestine, which is rich in immune cells. In addition, some of the live attenuated organisms (such as Shigella and Salmonella described above) that normally invade the intestinal epithelium are being tested both as vaccines and as delivery vectors for antigens from other pathogens.[10-13]

An approach that has great appeal in relation to the potential ease of both production and delivery is using

transgenic edible plants to make vaccines. For example, genes encoding antigens have been cloned into potato plants. The potato makes the protein, and hence by eating the potato, animals—and more recently humans—have been shown to develop immune responses.[14,15] The drawback of using potatoes is that they are usually eaten cooked, and this may denature a protein antigen. Thus, bananas are considered the ideal food base for a vaccine. Of course, fundamental questions still need to be addressed, since intestinal administration of some antigens in certain forms has proved to be an effective means of generating antigen-specific tolerance. But the appeal of making an edible vaccine, especially one that infants would enjoy receiving, is great. Another advantage is that agricultural production will probably be less costly than biological manufacturing.

One of the functions of skin has been presumed to be protection from direct entry of entities (whether pathogens or compounds) into the body. Yet, the transdermal patch has been an efficacious and patient-friendly means of delivering systemic drugs. Vaccines of the future may be delivered through the skin by patches or other needleless devices.[16] These approaches would not only provide an advantage from the recipient's perspective but also may be able to harness the wealth of antigen presenting cells in the skin.

Adjuvants

Adjuvants are compounds that increase the immunogenicity of a given vaccine. Alum has long been the only compound approved for human use, but a vaccine with an adjuvant known as MF59 was licensed recently.[17] In the future, MF59 and other compounds still in development (for example, LTK63, see above)[8,9,18] will be used even more widely to reduce the number of immunizations or increase the potency in people who otherwise would not respond.

CLINICAL TARGETS FOR VACCINES

Infectious diseases

There are still many diseases for which we need vaccines or better vaccines. The misuse of antibiotics has resulted in the increasing development of antibiotic-resistant strains of bacteria. Furthermore, as useful and effective as antiviral drugs have been, their limitations have been painfully obvious for agents such as hepatitis C virus and HIV, where the side effects or rigors of the treatment regimen, or both, reduce the number of people who are treated. Other problems, such as the cost of treatment and the limited population of patients who respond, also underline the continued need for vaccines. In addition to the future development of successful vaccines for pathogens such as HIV, hepatitis C virus, malaria, and herpes simplex virus, new vaccines will be made that will be more effective against pathogens such as M tuberculosis, for which a vaccine already exists. In addition, although all vaccines to date have been for prophylaxis, vaccines will be developed to treat infectious diseases. For example, since the immune response is clearly capable of clearing infection for a number of pathogens that can also cause chronic infection, it is logical to try to stimulate such a therapeutic immune response in individuals who have not succeeded to clear infection on their own. Examples of such vaccines under evaluation include ones for hepatitis B virus, hepatitis C virus, HIV, tuberculosis, and human papilloma virus infections.

Cancer

Cancer gene therapy in the future will probably include the gene-based delivery not only of anti-angiogenic molecules but also of tumor-specific antigens in conjunction with cytokines. Therapeutic cancer vaccines illustrate how the concept of vaccines has widened to encompass noninfectious diseases and treatment. Furthermore, cancer vaccines illustrate the increasing blur between the areas of gene therapy and vaccines. The vectors used for so-called gene vaccines, which consist of either a DNA plasmid or of a viral vector only, are also being used for some gene therapies.

Allergies

Efforts to harness the immune response and turn it in another direction are also being used to develop vaccines for allergies. For example, a type 2 T helper response (the production of cytokines such as interleukin 4 and interleukin 10, which are necessary for making antibody responses) versus a type 1 T helper response (cytokines such as interleukin 2 and γ interferon, which are particularly relevant for cellular responses) to particular antigens has been implicated in the pathogenesis of certain allergies and autoimmune states. Thus, vaccines are being developed to specifically manipulate the antigen-specific response to be predominantly a type 1 T helper response.

Other conditions

While gene therapists work toward curing diabetes through gene therapy, vaccinologists are striving to prevent or treat this and other autoimmune diseases by efforts to induce antigen-specific tolerance and by altering the immunologic milieu to change the type of immune response.

Chronic and metabolic diseases such as hypercholesterolemia are now targets for vaccine development. The prevention of pregnancy via vaccines has been an effort in many countries because of the long duration of immunity seen with traditional vaccines. Another new arena is the

treatment of addictions, such as smoking and drug misuse, via the generation of immune responses against nicotine and cocaine, for example.

SOCIAL FACTORS

Social factors have also had an impact on vaccine development. For example, more effort is being made to eliminate the need for syringe injections, in an effort to make vaccines both more accessible in parts of the world and more acceptable from the patient's perspective. Likewise, the knowledge that each year millions of children worldwide die from infectious diseases for which vaccines exist, has spurred efforts to make more stable vaccines that do not need refrigeration or devices for delivery. And finally, the very success of vaccines at eliminating untold morbidity and mortality and the increased understanding of immune responses have raised expectations to desire prevention or cure of a myriad of diseases in addition to infectious diseases. The proved value of vaccines, coupled with powerful new technologies, promise that they will have an increasing role in efforts to improve the health of the denizens, both human and animal, of the planet.

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Sensors in medicine

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Sensors are devices that detect physical, chemical and biological signals and provide a way for those signals to be measured and recorded.[1] Physical properties that can be sensed include temperature, pressure, vibration, sound level, light intensity, load or weight, flow rate of gases and liquids, amplitude of magnetic and electronic fields, and concentrations of many substances in gaseous, liquid, or solid form. Although sensors of today are where computers were in 1970, medical applications of sensors are taking off because of advances in microchip technologies and molecular chemistry.[2,3]

Sensors have played an important role in many industries, providing the mechanical "vision" used for counting, sorting, reading, and robotic guidance. Tactile sensors, typically piezoelectric materials, generate voltage when touched, squeezed, or bent, or when their temperature is changed. Other sensors can detect specific chemical pressures and fluid levels. Cars, homes, and offices are loaded with sensors. In the short term, sensors used in medical applications will emit a signal that can be read at the point of determination or transferred by wire or wireless transmission to remote locations. Advances in microprocessor technologies have created a smart sensor that unites sensing capability and data processing in a single integrated circuit chip. The next step is combining sensing and processing with an actuator, such as microelectromechanical systems.[4,5]